**Maintenance of General Anesthesia: Intermittent Bolus**

**Healthy Adults Less Than 55 Years of Age:** Increments of 20 to 50 mg as needed.

**Initiation of MAC Sedation**

**Healthy Adults Less Than 55 Years of Age:** Slow infusion or slow injection techniques are recommended to avoid apnea or hypotension. Most patients require an infusion of 100 to 150 μg/kg/min (6 to 9 mg/kg/h) for 3 to 5 minutes or a slow injection of 0.5 mg/kg over 3 to 5 minutes followed immediately by a maintenance infusion.

**Elderly, Debilitated, Neurosurgical, or ASA III/IV Patients:** Most patients require dosages similar to healthy adults. Rapid boluses are to be avoided (See WARNINGS.)

**Maintenance of MAC Sedation**

**Healthy Adults Less Than 55 Years of Age:** A variable rate infusion technique is preferable over an intermittent bolus technique. Most patients require an infusion of 25 to 75 μg/kg/min (1.5 to 4.5 mg/kg/h) or incremental bolus doses of 10 mg or 20 mg.

**In Elderly, Debilitated, Neurosurgical, or ASA III/IV Patients:** Most patients require 80% of the usual adult dose. A rapid (single or repeated) bolus dose should not be used. (See WARNINGS.)

**Initiation and Maintenance of ICU Sedation in Intubated, Mechanically Ventilated**

**Adult Patients**—Because of the lingering effects of previous anesthetic or sedative agents, in most patients the initial infusion should be 5 μg/kg/min (0.3 mg/kg/h) for at least 5 minutes. Subsequent increments of 5 to 10 μg/kg/min (0.3 to 0.6 mg/kg/h) over 5 to 10 minutes may be used until desired level of sedation is achieved. Maintenance rates of 5 to 50 μg/kg/min (0.3 to 3 mg/kg/h) or higher may be required. **Evaluation of level of sedation and assessment of CNS function should be carried out daily throughout maintenance to determine the minimum dose of DIPRIVAN Injectable Emulsion required for sedation.**

**The tubing and any unused portions of DIPRIVAN Injectable Emulsion should be discarded after 12 hours because DIPRIVAN Injectable Emulsion contains no preservatives and is capable of supporting growth of microorganisms. (See WARNINGS, and DOSAGE AND ADMINISTRATION.)**

**Compatibility and Stability:** DIPRIVAN Injectable Emulsion should not be mixed with other therapeutic agents prior to administration.

**Dilution Prior to Administration:** When DIPRIVAN Injectable Emulsion is diluted prior to administration, it should only be diluted with 5% Dextrose Injection, USP, and it should not be diluted to a concentration less than 2 mg/mL because it is an emulsion. In diluted form it has been shown to be more stable when in contact with glass than with plastic (95% potency after 2 hours of running infusion in plastic).

**Administration with Other Fluids:** Compatibility of DIPRIVAN Injectable Emulsion with the coadministration of blood/serum/plasma has not been established. (See WARNINGS.) DIPRIVAN Injectable Emulsion has been shown to be compatible when administered with the following intravenous fluids.

- 5% Dextrose Injection, USP
- Lactated Ringers Injection, USP
- Lactated Ringers and 5% Dextrose Injection
- 5% Dextrose and 0.45% Sodium Chloride Injection, USP
- 5% Dextrose and 0.2% Sodium Chloride Injection, USP

**Assembly Instructions for Pre-Filled Syringe**

1. Remove the Luer connector from packaging.
2. Remove glass syringe barrel from tray and check for cracks or leaks. Shake. Remove the blue plastic cover. Disinfect the rubber stopper using alcohol swab provided in package. Allow to dry.
3. Pull off needle cover from Luer connector. The bevel of the needle spike is slightly bent (c-tip) to prevent potential coring.
4. Stand the syringe barrel vertically on a hard surface and push Luer connector on to syringe barrel so needle penetrates rubber seal and connector slides over the blue seal until firmly seated. (Fig. 1)

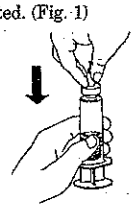
Fig.1

5. Add plunger rod by screwing clockwise. CAUTION: the rod must be fully screwed on, otherwise it may detach which could result in siphoning of the syringe contents. (Fig. 2)

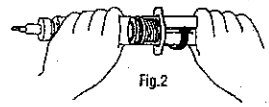
Fig.2

6. Unscrew Luer cover remove excess nitrogen gas from the syringe (a small nitrogen gas bubble may remain). Assemble administration line and connect syringe.

**Handling Procedures**

**General**

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Clinical experience with the use of in-line filters and DIPRIVAN Injectable Emulsion during anesthesia or ICU/MAC sedation is limited. DIPRIVAN Injectable Emulsion should only be administered through a filter with a pore size of 5 microns or greater unless it has been demonstrated that the filter does not restrict the flow of DIPRIVAN Injectable Emulsion and/or cause the breakdown of the emulsion. Filters should be used with caution and where clinically appropriate. Continuous monitoring is necessary due to the potential for restricted flow and/or breakdown of the emulsion. Do not use if there is evidence of separation of the phases of the emulsion.

Rare cases of self-administration of DIPRIVAN Injectable Emulsion, by health care professionals have been reported, including some fatalities (See DRUG ABUSE AND DEPENDENCE).

**STRICT ASEPTIC TECHNIQUE MUST ALWAYS BE MAINTAINED DURING HANDLING. DIPRIVAN INJECTABLE EMULSION IS A SINGLE-USE PARENTERAL PRODUCT; WHICH CONTAINS 0.005% DISODIUM EDETATE TO RETARD THE RATE OF GROWTH OF MICROORGANISMS IN THE EVENT OF ACCIDENTAL EXTRINSIC CONTAMINATION. HOWEVER, DIPRIVAN INJECTABLE EMULSION CAN STILL SUPPORT THE GROWTH OF MICROORGANISMS AS IT IS NOT AN ANTIMICROBIALLY PRESERVED PRODUCT UNDER USP STANDARDS. ACCORDINGLY, STRICT ASEPTIC TECHNIQUE MUST STILL BE ADHERED TO. DO NOT USE IF CONTAMINATION IS SUSPECTED. DISCARD UNUSED PORTIONS AS DIRECTED WITHIN THE REQUIRED TIME LIMITS (SEE DOSAGE AND ADMINISTRATION, HANDLING PROCEDURES). THERE HAVE BEEN REPORTS IN WHICH FAILURE TO USE ASEPTIC TECHNIQUE WHEN HANDLING DIPRIVAN INJECTABLE EMULSION WAS ASSOCIATED WITH MICROBIAL CONTAMINATION OF THE PRODUCT AND WITH FEVER, INFECTION/SEPSIS, OTHER LIFE-THREATENING ILLNESS, AND/OR DEATH.**

**Guideline for Aseptic Technique for General Anesthesia/MAC Sedation**

DIPRIVAN Injectable Emulsion should be prepared for use just prior to initiation of each individual anesthetic/sedative procedure. The ampule neck surface, or vial/pre-filled syringe rubber stopper should be disinfected using 70% isopropyl alcohol. DIPRIVAN Injectable Emulsion should be drawn into sterile syringes immediately after ampules or vials are opened. When withdrawing DIPRIVAN Injectable Emulsion from vials, a sterile vent spike should be used. The syringe(s) should be labeled with appropriate information including the date and time the ampule or vial was opened. Administration should commence promptly and be completed within 6 hours after the ampules, vials, or pre-filled syringes have been opened.

DIPRIVAN Injectable Emulsion should be prepared for single patient use only. Any unused portions of DIPRIVAN Injectable Emulsion, reservoirs, dedicated administration tubing and/or solutions containing DIPRIVAN Injectable Emulsion must be discarded at the end of the anesthetic procedure or at 6 hours, whichever occurs sooner. The IV line should be flushed every 6 hours and at the end of the anesthetic procedure to remove residual DIPRIVAN Injectable Emulsion.

**Guidelines for Aseptic Technique for ICU Sedation**

When DIPRIVAN Injectable Emulsion is administered directly from the vial, strict aseptic techniques must be followed. The vial rubber stopper should be disinfected using 70% isopropyl alcohol. A sterile vent spike and sterile tubing must be used for administration of DIPRIVAN Injectable Emulsion. As with other lipid emulsions, the number of IV line manipulations should be minimized. Administration should commence promptly and must be completed within 12 hours after the vial has been spiked. The tubing and any unused portions of DIPRIVAN Injectable Emulsion must be discarded after 12 hours.

If DIPRIVAN Injectable Emulsion is transferred to a syringe or other container prior to administration, the handling procedures for General anesthesia/MAC sedation should be followed, and the product should be discarded and administration lines changed after 6 hours.

## HOW SUPPLIED

DIPRIVAN Injectable Emulsion is available in ready to use 20 mL ampules, 50 mL infusion vials, 100 mL infusion vials, and 50 mL pre-filled syringes containing 10 mg/mL of propofol.

20 mL ampules (NDC 0310-0300-20)
50 mL infusion vials (NDC 0310-0300-50)
100 mL infusion vials (NDC 0310-0300-11)
50 mL pre-filled syringes (NDC 0310-0300-54)

Propofol undergoes oxidative degradation, in the presence of oxygen, and is therefore packaged under nitrogen to eliminate this degradation path.

Store between 4°–22°C (40°–72° F). Refrigeration is not recommended. Shake well before use.

Manufactured for:
**ZENECA**
**Pharmaceuticals**
A Business Unit of Zeneca Inc.
Wilmington, Delaware 19850-5437
64090-01 Rev D 06/96

*Shown in Product Identification Guide, page 341*

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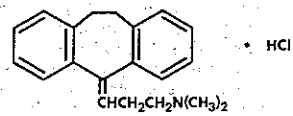
**ELAVIL®** ℞
**(AMITRIPTYLINE HCl)**
**Tablets and Injection**

## DESCRIPTION

Amitriptyline HCl is 3-(10,11-dihydro-5*H*-dibenzo [a,*d*] cycloheptene-5-ylidene)-*N*,*N*-dimethyl-1-propanamine hydrochloride. Its empirical formula is $C_{20}H_{23}N \bullet HCl$ and its structual formula is:




Amitriptyline HCl, a dibenzocycloheptadiene derivative, has a molecular weight of 313.87. It is a white, odorless, crystalline compound which is freely soluble in water.

ELAVIL* (Amitriptyline HCl) is supplied as 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, and 150 mg tablets and as a sterile solution for intramuscular use. Inactive ingredients of the tablets are calcium phosphate, cellulose, colloidal silicon dioxide, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, starch, stearic acid, talc, and titanium dioxide. Tablets ELAVIL 10 mg also contain FD&C Blue 1. Tablets ELAVIL 25 mg also contain D&C Yellow 10, FD&C Blue 1, and FD&C Yellow 6. Tablets ELAVIL 50 mg also contain D&C Yellow 10, FD&C Yellow 6 and iron oxide. Tablets ELAVIL 75 mg also contain FD&C Yellow 6. Tablets ELAVIL 100 mg also contain FD&C Blue 2 and FD&C Red 40. Tablets ELAVIL 150 mg also contain FD&C Blue 2 and FD&C Yellow 6. Each milliliter of the sterile solution contains:

| | |
|---|---|
| Amitriptyline hydrochloride | 10 mg |
| Dextrose | 44 mg |
| Water for Injection, q.s | 1 mL |
| Added as preservatives: | |
| Methylparabel | 1.5 mg |
| Propylparaben | 0.2 mg |

## ACTIONS

ELAVIL is an antidepressant with sedative effects. Its mechanism of action in man is not known. It is not a monoamine oxidase inhibitor and it does not act primarily by stimulation of the central nervous system.

Amitriptyline inhibits the membrane pump mechanism responsible for uptake of norepinephrine and serotonin in adrenergic and serotonergic neurons. Pharmacologically this action may potentiate or prolong neuronal activity since reuptake of this biogenic amines is important physiologically in terminating transmitting activity. This interference with the reuptake of norepinephrine and/or serotonin is believed by some to underlie the antidepressant activity of amitriptyline.

## INDICATIONS

For the relief of symptoms of depression. Endogenous depression is more likely to be alleviated than are other depressive states.

## CONTRAINDICATIONS

ELAVIL is contraindicated in patients who have shown prior hypersensitivity to it.

It should not be given concomitantly with monoamine oxidase inhibitors. Hyperpyretic crises, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressant and monoamine oxidase inhibiting drugs simulta-

***Continued on next page***

## Zeneca Pharmaceuticals—Cont.

neously. When it is desired to replace a monoamine oxidase inhibitor with ELAVIL, a minimum of 14 days should be allowed to elapse after the former is discontinued. ELAVIL should then be initiated cautiously with gradual increase in dosage until optimum response is achieved.

This drug is not recommended for use during the acute recovery phase following myocardial infarction.

### WARNINGS

ELAVIL may block the antihypertensive action of guanethidine or similarly acting compounds.

It should be used with caution in patients with a history of seizures and, because of its atropine-like action, in patients with a history of urinary retention, angle-closure glaucoma or increased intraocular pressure. In patients with angle-closure glaucoma, even average doses may precipitate an attack.

Patients with cardiovascular disorders should be watched closely. Tricyclic antidepressant drugs, including ELAVIL, particularly when given in high doses, have been reported to produce arrhythmias, sinus tachycardia, and prolongation of the conduction time. Myocardial infarction and stroke have been reported with drugs of this class.

Close supervision is required when ELAVIL is given to hyperthyroid patients or those receiving thyroid medication.

ELAVIL may enhance the response to alcohol and the effects of barbituates and other CNS depressants. In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdosage. Delirium has been reported with concurrent administration of amitriptyline and disulfiram.

**Usage in Pregnancy:** Teratogenic effects were not observed in mice, rats, or rabbits when amitriptyline was given orally at doses of 2 to 40 mg/kg/day (up to 13 times the maximum recommended human dose**). Studies in literature have shown amitriptyline to be teratogenic in mice and hamsters when given by various routes of administration at doses of 28 to 100 mg/kg/day (9 to 33 times the maximum recommended human dose), producing multiple malformations. Another study in the rat reported that an oral dose of 25 mg/kg/day (8 times the maximum recommended human dose) produced delays in ossification of fetal vertebral bodies without other signs of embryotoxicity. In rabbits, an oral dose of 60 mg/kg/day (20 times the maximum recommended human dose) was reported to cause incomplete ossification of the cranial bones.

Amitriptyline has been shown to cross the placenta. Although a causal relationship has not been established, there have been a few reports of adverse events, including CNS effects, limb deformities, or developmental delay, in infants whose mothers had taken amitriptyline during pregnancy.

There are no adequate and well-controlled studies in pregnant women. ELAVIL should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

**Nursing Mothers:** Amitriptyline is excreted into breast milk. In one report in which a patient received amitriptyline 100 mg/day while nursing her infant, levels of 83–141 ng/mL were detected in the mother's serum. Levels of 135–151 ng/mL were found in the breast milk, but no trace of the drug could be detected in the infant's serum.

Because of the potential for serious adverse reactions in nursing infants from amitriptyline, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

**Usage in Children:** In view of the lack of experience with the use of this drug in children, it is not recommended at the present time for patients under 12 years of age.

### PRECAUTIONS

Schizophrenic patients may develop increased symptoms of psychosis; patients with paranoid symptomatology may have an exaggeration of such symptoms. Depressed patients, particularly those with known manic-depressive illness, may experience a shift to mania or hypomania. In these circumstances the dose of amitriptyline may be reduced or a major tranquilizer such as perphenazine may be administered concurrently.

The possibility of suicide in depressed patients remains until significant remission occurs. Potentially suicidal patients should not have access to large quantities of this drug. Prescriptions should be written for the smallest amount feasible.

Concurrent administration of ELAVIL and electroshock therapy may increase the hazards associated with such therapy. Such treatment should be limited to patients for whom it is essential.

When possible, the drug should be discontinued several days before elective surgery.

Both elevation and lowering of blood sugar levels have been reported.

ELAVIL should be used with caution in patients with impared liver function.

**Drug Interactions:** Drugs Metabolized by P450 2D6—The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the caucasian population (about 7–10% of caucasians are so called "poor metabolizers"); reliable estimates of the prevalance of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafenone and flecainidine). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be coadministered with another drug known to be an inhibitor of P450 2D6.

Monoamine oxidase inhibitors—see CONTRAINDICATIONS section. Guanethidine or similarly acting compounds; thyroid medication; alcohol, barbiturates and other CNS depressants; and disulfiram—see WARNINGS section.

When ELAVIL is given with anticholinergic agents or sympathomimetic drugs, including epinephrine combined with local anesthetics, close supervision and careful adjustment of dosages are required.

Hyperpyrexia has been reported when ELAVIL is administered with anticholinergic agents or with neuroleptic drugs, particularly during hot weather.

Paralytic ileus may occur in patients taking tricyclic antidepressants in combination with anticholinergic-type drugs.

Cimetidine is reported to reduce hepatic metabolism of certain tricyclic antidepressants, thereby delaying elimination and increasing steady-state concentrations of these drugs. Clinically significant effects have been reported with the tricyclic antidepressants when used concomitantly with cimetidine. Increases in plasma levels of tricyclic antidepressants, and in the frequency and severity of side effects, particularly anticholinergic, have been reported when cimetidine was added to the drug regimen. Discontinuation of cimetidine in well-controlled patients receiving tricyclic antidepressants and cimetidine may decrease the plasma levels and efficacy of the antidepressants.

Caution is advised if patients receive large doses of ethchlorvynol concurrently. Transient delirium has been reported in patients who were treated with one gram of ethchlorvynol and 75–150 mg of ELAVIL.

**Information for Patients:** While on therapy with ELAVIL, patients should be advised as to the possible impairment of mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

### ADVERSE REACTIONS

Within each category the following adverse reactions are listed in order of decreasing severity. Included in the listing are a few adverse reactions which have not been reported with this specific drug. However, pharmacological similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when amitriptyline is administered.

**Cardiovascular:** Myocardial infarction; stroke; nonspecific ECG changes and changes in AV conduction; heart block; arrhythmias; hypotension, particularly orthostatic hypotension; syncope; hypertension; tachycardia; palpitation.

**CNS and Neuromuscular:** Coma; seizures; hallucinations; delusions; confusional states; disorientation; incoordination; ataxia; tremors; peripheral neuropathy; numbness, tingling, and paresthesias of the extremities; extrapyramidal symptoms including abnormal involuntary movements and tardive dyskinesia; dysarthria; disturbed concentration; excitement; anxiety; insomnia; restlessness; nightmares; drowsiness; dizziness; weakness; fatigue; headache; syndrome of inappropriate ADH (antidiuretic hormone) secretion; tinnitus; alteration in EEG patterns.

**Anticholinergic:** Paralytic ileus; hyperpyrexia; urinary retention; dilatation of the urinary tract; constipation; blurred vision, disturbance of accommodation, increased ocular pressure, mydriasis; dry mouth.

**Allergic:** Skin rash; urticaria, photosensitization; edema of face and tongue.

**Hematologic:** Bone marrow depression including agranulocytosis, leukopenia, thrombocytopenia; purpura; eosinophilia.

**Gastrointestinal:** Rarely hepatitis (including altered liver function and jaundice); nausea; epigastric distress; vomiting; anorexia; stomatitis, peculiar taste; diarrhea; parotid swelling; black tongue.

**Endocrine:** Testicular swelling and gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido; impotence; elevation and lowering of blood sugar levels.

**Other:** Alopecia; edema; weight gain or loss; urinary frequency; increased perspiration.

**Withdrawal Symptoms:** After prolonged administration, abrupt cessation of treatment may produce nausea, headache, and malaise. Gradual dosage reduction has been reported to produce, within two weeks, transient symptoms including irritability, restlessness, and dream and sleep disturbance.

These symptoms are not indicative of addiction. Rare instances have been reported of mania or hypomania occurring within 2–7 days following cessation of chronic therapy with tricyclic antidepressants.

**Causal Relationship Unknown:** Other reactions, reported under circumstances where a causal relationship could not be established, are listed to serve as alerting information to physicians:

**Body as a Whole:** Lupus-like syndrome (migratory arthritis, positive ANA and rheumatoid factor).

**Digestive:** Hepatic failure, ageusia.

### DOSAGE AND ADMINISTRATION

**Oral Dosage**

Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerance.

**Initial Dosage for Adults:** For outpatients 75 mg of amitriptyline HCl a day in divided doses is usually satisfactory. If necessary, this may be increased to a total of 150 mg per day. Increases are made preferably in the late afternoon and/or bedtime doses. A sedative effect may be apparent before the antidepressant effect is noted, but an adequate therapeutic effect may take as long as 30 days to develop.

An alternate method of initiating therapy in outpatients is to begin with 50 to 100 mg amitriptyline HCl at bedtime. This may be increased by 25 or 50 mg as necessary in the bedtime dose to a total of 150 mg per day.

Hospitalized patients may require 100 mg a day initially. This can be increased gradually to 200 mg a day if necessary. A small number of hospitalized patients may need as much as 300 mg a day.

**Adolescent and Elderly Patients:** In general, lower dosages are recommended for these patients. Ten mg 3 times a day with 20 mg at bedtime may be satisfactory in adolescent and elderly patients who do not tolerate higher dosages.

**Maintenance:** The usual maintenance dosage of amitriptyline HCl is 50 to 100 mg per day. In some patients 40 mg per day is sufficient. For maintenance therapy the total daily dosage may be given in a single dose preferably at bedtime. When satisfactory improvement has been reached, dosage should be reduced to the lowest amount that will maintain relief of symptoms. It is appropriate to continue maintenance therapy 3 months or longer to lessen the possibility of relapse.

**Intramuscular Dosage**

Initially, 20 to 30 mg (2 to 3 mL) four times a day.

When ELAVIL Injection is administered intramuscularly, the effects may appear more rapidly than with oral administration.

When ELAVIL Injection is used for initial therapy in patients unable or unwilling to take ELAVIL Tablets, the tablets should replace the injection as soon as possible.

**Usage in Children**

In view of the lack of experience with the use of this drug in children, it is not recommended at the present time for patients under 12 years of age.

**Plasma Levels**

Because of the wide variation in the absorption and distribution of tricyclic antidepressants in body fluids, it is difficult to directly correlate plasma levels and therapeutic effect. However, determination of plasma levels may be useful in identifying patients who appear to have toxic effects and may have excessively high levels, or those in whom lack of absorption or noncompliance is suspected. Adjustments in

dosage should be made according to the patient's clinical response and not on the basis of plasma levels.***

## OVERDOSAGE

Deaths may occur from overdosage with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate tricyclic antidepressant overdosage. As the management is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. Signs and symptoms of toxicity develop rapidly after tricyclic antidepressant overdose, therefore, hospital monitoring is required as soon as possible.

**Manifestations:** Critical manifestations of overdose include: cardiac dysrhythmias, severe hypotension, convulsions, and CNS depression, including coma. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of tricyclic antidepressant toxicity.

Other signs of overdose may include: impaired myocardial contractility, confusion; disturbed concentration, transient visual hallucinations, dilated pupils, disorders of ocular motility, agitation, hyperactive reflexes, polyradiculoneuropathy, stupor, drowsiness, muscle rigidity, vomiting, hypothermia, hyperpyrexia, or any of the symptoms listed under ADVERSE REACTIONS.

**Management:**

**General:** Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line and initiate gastric decontamination. A minimum of six hours of observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during the period, extended monitoring is required. There are case reports of patients succumbing to fatal dysrhythmias late after overdose; these patients had clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination. Monitoring of plasma drug levels should not guide management of the patient.

**Gastrointestinal Decontamination:** All patients suspected of tricyclic antidepressant overdose should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. Emesis is contraindicated.

**Cardiovascular:** A maximal limb-lead QRS duration of $\geq 0.10$ seconds may be the best indication of the severity of the overdose. Intravenous sodium bicarbonate should be used to maintain the serum pH in the range of 7.45 to 7.55. If the pH response is inadequate, hyperventilation may also be used. Concomitant use of hyperventilation and sodium bicarbonate should be done with extreme caution, with frequent pH monitoring. A pH $> 7.60$ or a $pCO_2 < 20$ mm Hg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium or phenytoin. Type 1A and 1C antiarrhyghmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide).

In rare instances, hemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, hemodialysis, peritoneal dialysis, exchange tranfusions, and forced diuresis generally have been reported as ineffective in tricyclic antidepressant poisoning.

**CNS:** In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines, or if these are ineffective, other anticonvulsants, (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in consultation with a poison control center.

**Psychiatric Follow-up:** Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

**Pediatric Managment:** The principles of management of pediatric and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

## HOW SUPPLIED

Tablets ELAVIL, 10 mg, are blue, round, film coated tablets, identified with "40" debossed on one side and "ELAVIL" on the other side. They are supplied as follows:
NDC 0310-0040-10 bottles of 100
NDC 0310-0040-34 bottles of 1000
Tablets ELAVIL, 25 mg, are yellow, round, film coated tablets, identified with "45" debossed on one side and "ELAVIL" on the other side. They are supplied as follows:
NDC 0310-0045-10 bottles of 100
NDC 0310-0045-39 unit dose packages of 100
NDC 0310-0045-34 bottles of 1000
NDC 0310-0045-50 bottles of 5000
Tablets ELAVIL, 50 mg, are beige, round, film coated tablets, identified with "41" debossed on one side and "ELAVIL" on the other side. They are supplied as follows:
NDC 0310-0041-10 bottles of 100
NDC 0310-0041-39 unit dose packages of 100
NDC 0310-0041-34 bottles of 1000
Tablets ELAVIL, 75 mg, are orange, round, film coated tablets, identified with "42" debossed on one side and "ELAVIL" on the other side. They are supplied as follows:
NDC 0310-0042-10 bottles of 100
Tablets ELAVIL, 100 mg, are mauve, round, film coated tablets, identified with "43" debossed on one side and "ELAVIL" on the other side. They are supplied as follows:
NDC 0310-0043-10 bottles of 100
Tablets ELAVIL, 150 mg, are blue, capsule shaped, film coated tablets, identified with "47" debossed on one side and "ELAVIL" on the other side. They are supplied as follows:
NDC 0310-0047-30 bottles of 30
NDC 0310-0047-10 bottles of 100
Injection ELAVIL, 10 mg/mL, is a clear, colorless solution, and is supplied as follows:
NDC 0310-0049-10 in 10 mL vials

**Storage:** Store Tablets ELAVIL in a well-closed container. Avoid storage at temperatures above 30°C (86°F). In addition, Tablets ELAVIL 10 mg must be protected from light and stored in a well-closed, light-resistant container.

Protect ELAVIL Injection from freezing and avoid storage above 30°C (86°F).

## METABOLISM

Studies in man following oral administration of $^{14}C$-labeled drug indicated at amitriptyline is rapidly absorbed and metabolized. Radioactivity of the plasma was practically negligible, although significant amounts of radioactivity appeared in the urine by 4 to 6 hours and one-half to one-third of the drug was excreted within 24 hours.

Amitriptyline is metabolized by N-demethylation and bridge hydroxulation in man, rabbit, and rat. Virtually the entire dose is excreted as glucuronide or sulfate conjugate of metabolites, with little unchanged drug appearing in the urine. Other metabolic pathways may be involved.

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*Registered trademark of ZENECA Inc.

**Based on a maximum recommended amitripyline dose of 150 mg/day or 3 mg/kg/day for a 50 kg patient.

***Hollister LE: JAMA 1979;241:2350–2533.

Manufactured for:
**ZENECA Pharmaceuticals**
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Wilmington, Delaware 19850-5437
by MERCK & Co., Inc., West Point, PA 19486, USA
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*Shown in Product Identification Guide, page 341*

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**HIBICLENS® Antiseptic/Antimicrobial** **OTC**
[*hi'bi-klenz*]
**Skin Cleanser**
**(chlorhexidine gluconate)**

## DESCRIPTION

HIBICLENS is an antiseptic antimicrobial skin cleanser possessing bactericidal activities. HIBICLENS contains 4% w/v HIBITANE® (chlorhexidine gluconate), a chemically unique hexamethylenebis biguanide with inactive ingredients: Fragrance, isopropyl alcohol 4%, purified water, Red 40, and other ingredients, in a mild, sudsing base adjusted to pH 5.0–6.5 for optimal activity and stability as well as compatibility with the normal pH of the skin.

## ACTION

HIBICLENS is bactericidal on contact. It has antiseptic activity and a persistent antimicrobial effect with rapid bactericidal activity against a wide range of microorganisms, including gram-positive bacteria, and gram-negative bacteria such as *Pseudomonas aeruginosa.* The effectiveness of HIBICLENS is not signficantly reduced by the presence of organic matter, such as blood.[1]

In a study[2] simulating surgical use, the immediate bactericidal effect of HIBICLENS after a single six-minute scrub resulted in a 99.9% reduction in resident bacterial flora, with a reduction of 99.98% after the eleventh scrub. Reductions on surgically gloved hands were maintained over the six-hour test period.

HIBICLENS displays persistent antimicrobial action. In one study[2], 93% of a radiolabeled formulation of HIBICLENS remained present on uncovered skin after five hours.

HIBICLENS prevents skin infection thereby reducing the risk of cross-infection.

## INDICATIONS

HIBICLENS is indicated for use as a surgical scrub, as a health-care personnel handwash, for patient preoperative showering and bathing, as a patient preoperative skin preparation, and as a skin wound cleanser and general skin cleanser.

## SAFETY

The extensive use of chlorhexidine gluconate for over 20 years outside the United States has produced no evidence of absorption of the compound through intact skin. The potential for producing skin reactions is extremely low. HIBICLENS can be used many times a day without causing irritation, dryness, or discomfort. Experimental studies indicate that when used for cleaning superficial wounds, HIBICLENS will neither cause additional tissue injury nor delay healing.

## WARNINGS

**FOR EXTERNAL USE ONLY. KEEP OUT OF EYES, EARS AND MOUTH. HIBICLENS SHOULD NOT BE USED AS A PREOPERATIVE SKIN PREPARATION OF THE FACE OR HEAD. MISUSE OF HIBICLENS HAS BEEN REPORTED TO CAUSE SERIOUS AND PERMANENT EYE INJURY WHEN IT HAS BEEN PERMITTED TO ENTER AND REMAIN IN THE EYE DURING SURGICAL PROCEDURES. IF HIBICLENS SHOULD CONTACT THESE AREAS, RINSE OUT PROMPTLY AND THOROUGHLY WITH WATER.**

Avoid contact with meninges. HIBICLENS should not be used by persons who have a sensitivity to it or its components. Chlorhexidine gluconate has been reported to cause deafness when instilled in the middle ear through perforated ear drums. Irritation, sensitization and generalized allergic reactions have been reported with chlorhexidine-containing products, especially in the genital areas. If adverse reactions occur, discontinue use immediately and if severe, contact a physician. Keep this and all drugs out of the reach of children. In case of accidental ingestion, seek professional assistance or contact a Poison Control Center immediately.

*Accidental ingestion:* Chlorhexidine gluconate taken orally is poorly absorbed. Treat with gastric lavage using milk, egg white, gelatin or mild soap. Employ supportive measures as appropriate.

Avoid excessive heat (above 104°F).

## DIRECTIONS FOR USE

**Skin Wound and General skin Cleansing**

Wounds which involve more than the superficial layers of the skin should not be routinely treated with HIBICLENS. HIBICLENS should not be used for repeated general skin cleansing of large body areas except in those patients whose underlying condition makes it necessary to reduce the bacterial population of the skin. To use, thoroughly rinse the area to be cleansed with water. Apply the minimum amount of HIBICLENS necessary to cover the skin or wound area and wash gently. Rinse again thoroughly.

**Preoperative Skin Preparation**

Apply HIBICLENS liberally to surgical site and swab for at least two minutes. Dry with a sterile towel. Repeat procedure for an additional two minutes and dry with a sterile towel.

**Preoperative Showering and Whole-Body bathing**

The patient should be instructed to wash the entire body, including the scalp, on two consecutive occasions immediately prior to surgery. Each procedure should consist of two consecutive thorough applications of HIBICLENS followed by thorough rinsing. If the patient's condition allows, showering is recommended for whole-body bathing. The recommended procedure is: Wet the body, including hair. Wash the

*Continued on next page*